Elevated Effort Cost Identified by Computational Modeling as a Distinctive Feature Explaining Multiple Behaviors in Patients With Depression

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ABSTRACT

BACKGROUND: Motivational deficit is a core clinical manifestation of depression and a strong predictor of treatment failure. However, the underlying mechanisms, which cannot be accessed through conventional questionnaire-based scoring, remain largely unknown. According to decision theory, apathy could result either from biased subjective estimates (of action costs or outcomes) or from dysfunctional processes (in making decisions or allocating resources).

METHODS: Here, we combined a series of behavioral tasks with computational modeling to elucidate the motivational deficits of 35 patients with unipolar or bipolar depression under various treatments compared with 35 matched healthy control subjects.

RESULTS: The most striking feature, which was observed independent of medication across preference tasks (likeability ratings and binary decisions), performance tasks (physical and mental effort exertion), and instrumental learning tasks (updating choices to maximize outcomes), was an elevated sensitivity to effort cost. By contrast, sensitivity to action outcomes (reward and punishment) and task-specific processes were relatively spared.

CONCLUSIONS: These results highlight effort cost as a critical dimension that might explain multiple behavioral changes in patients with depression. More generally, they validate a test battery for computational phenotyping of motivational states, which could orientate toward specific medication or rehabilitation therapy, and thereby help pave the way for more personalized medicine in psychiatry.

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"Nature has placed mankind under the governance of two sovereign masters, pain and pleasure" (1). In this famous statement from Jeremy Bentham, mood is classically conceived as oscillating between the two extremes of pleasure and pain (2). Consistently, standard descriptions of mood disorders such as depression focused on the psychic pain (3) experienced by patients or their anhedonia (4), i.e., their inability to experience pleasure. However, for Bentham, a pioneer of utilitarian decision theory, pain and pleasure are masters in the sense that they drive behavior: people essentially strive to enjoy pleasure and to avoid experiencing pain. In this regard, patients with depression are not normally driven; their motivational deficit has recently emerged as a pathological cornerstone of depression. A key reason is that motivational deficit is one of the best predictors of functional impairment and subjective quality of life in depression (5,6). Another is that motivational deficit remains less responsive to conventional treatment than standard mood-related symptoms. For instance, the interest-activity dimension of clinical questionnaires is a strong predictor of poor response to antidepressants above and beyond depression severity (7). Moreover, motivational deficit is frequently reported as a residual symptom after adequate treatment by serotonergic antidepressants in unipolar depression or by mood stabilizers in bipolar disorder (8). Finally, motivational deficit could contribute to other dimensions of depression such as executive dysfunction and account for reduced efficiency in cognitive tests (9).

However, the way in which motivational deficit is assessed in current textbooks or clinical questionnaires does not align with modern decision theory. In this theory, the agent is supposed to engage in action that maximizes a cost/benefit tradeoff. The benefits relate to the outcome of the action, i.e., obtaining a reward or avoiding a punishment. The costs may relate to the action itself, such as effort, or modulate the value of the outcome, such as delay. In this view, items such as reduced activity or concentration difficulty (lack of engagement) would be the consequence of either low energy (higher expected effort cost) or low interest (lower expected reward value). Indeed, reduction of goal-directed behavior could result either from a decreased sensitivity to outcomes ("I do nothing because I see no purpose in potential activities") or from an increased sensitivity to effort ("I do nothing because the costs of actions are too high, even if the pleasures and pains at stake are still meaningful to me") (10,11).

Thus, in this view, effort is an attribute of actions that should be distinguished from punishment (or loss), which, similar to reward (or gain), is an attribute of outcomes. This distinction was observed by Bentham himself, who listed effort among the 9 pains of the senses, insisting on the "uneasy sensation which is apt to accompany any intense effort, whether of mind or body." Even today, effort stricto sensu is virtually absent from modern definitions of depression, although it is sometimes alluded to through the notions of fatigue or lack of energy. However, as stated in the DSM-5, patients with depression often report that even the smallest tasks seem to require substantial effort, while the efficiency with which tasks are accomplished may be reduced (12). These descriptions suggest that effort cost is increased in depression, which leads patients either to have a more aversive sensation if they invest the same effort as healthy people, or to be less efficient than healthy people if they match the aversive sensation by investing less effort.

The aim of this study is to properly dissociate the impact of depression on the sensitivity to effort, punishment, and reward, as conceptualized in decision theory. Note that we opted for the words reward/punishment because they designate outcomes of actions rather than gain/loss, which refer to changes in wealth that can be passively experienced (as with lotteries). To go beyond what clinical questionnaires can tell us (13) and to assess the integrity of motivational control processes, we set up a battery of behavioral tasks. This is important not only because questionnaires do not exactly assess the dimensions that are key to behavioral control, but also because they rely heavily on the quality of insight. In addition, behavioral tests present the advantage that they can be paralleled in animal models, opening an avenue for more invasive investigations of the neurophysiological mechanisms that may be dysfunctional in patients.

In brief, two main kinds of behavioral tasks have been used to assess motivational impairment in depression. One line of research has focused on reward versus punishment processing, typically using reinforcement learning paradigms (14). Classical results in depression suggest a reduced sensitivity to reward (15–17), which has been linked to anhedonia and dopaminergic transmission (18). Results regarding sensitivity to punishments are less consistent, with some studies showing worse performance following negative outcomes and others showing blunted responses to negative stimuli (19–24). In another line of research focused on the effort/reward trade-off, the effort dimension was first introduced with an incentive motivation test assessing the force exerted on a handgrip device as a function of the amount of money at stake (25). Since this seminal paper, reduced willingness to exert effort for reward has been reported in many studies using different behavioral readouts (binary choice, willingness to engage effort, effort-dependent performance) and different kinds of efforts (key pressing, handgrip squeezing, cognitive control tasks) (26–29) in various clinical populations (subsyndromal vs. actual depression, unipolar vs. bipolar depression, and drug-naïve patients) (28,29). A reward/effort trade-off task has also been used recently to predict relapse after antidepressant discontinuation (30).

While they made an important breakthrough, these studies have limitations. First, they typically used a unique behavioral task, thus taking the risk that results may depend on some specific task features that may not generalize across different contexts (e.g., the nature of reward, usually money, or the mode of response, usually choice). Second, they typically contrasted positive and negative dimensions, such as reward versus punishment or reward versus effort, failing to assess whether 2 negative dimensions such as effort and punishment are differentially affected in depression. Third, they seldom used mechanistic models that would help pinpoint the covert dysfunctional process, e.g., whether a reduced willingness to work is due to decreased sensitivity to reward or increased sensitivity to effort.

Toward this aim, a promising approach consists of phenotyping motivation states by fitting computational models to patients' behavior (31,32). Crucially, this computational approach can be used to discriminate between several cognitive dysfunctions that may result in a similar overt behavioral deficit (33), hence bridging the gap between clinical assessment and the underlying pathophysiology (34,35).

Using this approach, we assessed the behavior of patients with depression (n = 35, major depressive episode [MDE] group) and matched healthy control (HC) subjects (n = 35, HC group) in a comprehensive battery of preference, performance, and learning tasks that involved 2 types of outcome (reward and punishment) and 2 types of cost (effort and delay). The behavior of patients and HC subjects was then compared using computational models that tracked dysfunctional processing of the same motivational factor across different tasks.

METHODS AND MATERIALS

Participants

The study was approved by the local Ethics Committee (CPP Ile de France 3, Paris, France). A total of 70 participants completed the study, including 35 patients with depression and 35 HC subjects. All participants were informed that they would not be paid for their voluntary participation and that the monetary earnings in the task were purely fictive.

Patients were recruited in inpatient and outpatient facilities. They all met criteria for MDE, with a Montgomery–Åsberg Depression Rating Scale score $>$ 20 and a background diagnosis of either bipolar disorder or major depressive disorder (single or recurrent episode). Patients with a diagnosis of schizoaffective disorder were excluded. The HC group was recruited from the community. All participants were native French speakers, had normal or corrected-to-normal vision, and gave informed consent before taking part. The MDE and HC groups had no history of brain injury, epilepsy, alcohol or other drug abuse, or neurological disorders. The HC group was also screened for any history of psychiatric conditions, psychoactive substance abuse or dependence, or psychotropic medication use. There was no significant difference between the MDE group and the HC group regarding age, gender, or education level (Table 1).

The MDE group included both patients with bipolar disorder (n = 15) and patients with major depressive disorder (n = 20, single or recurrent episode). Note that the 2 subgroups are not matched and that our sample is underpowered to assess any

Table 1. Demographic and Psychometric Details

Characteristic	MDE Group, *n* = 35	HC Group, *n* = 35	*p* Value
Gender, Female/Male	18/17	18/17	1
Age, Years	42.5 (16.9)	43 (16.3)	.902
Education, Years	15.2 (3.8)	15.1 (2.5)	.881
Currently Active[a]	21	31	.116
PCSA, cm^2	43.0 (10.6)	43.2 (10.0)	.929
MADRS, Depression	36.1 (7.4)	2.9 (2.8)	<.001
Starkstein, Apathy	23.8 (5.6)	7.4 (4.0)	<.001
SHAPS, Anhedonia	5.4 (4.3)	0.5 (1.0)	<.001
Thase and Rush Staging	6/15/9/5	NA	–

Data are presented as *n* or mean (SD).

HC, healthy control; MADRS, Montgomery–Åsberg Depression Rating Scale; MDE, major depression episode; NA, not applicable; PCSA, physiological cross-sectional area (morphological proxy for maximal force, see the Supplement); SHAPS, Snaith-Hamilton Pleasure Scale.

[a]Including patients on sick leave and students.

differences between diagnoses. We nevertheless report demographic, psychometric, and treatment details separately for the 2 conditions (Table 2).

Experiment

All details about behavioral tasks and computational models can be found in the Supplemental Methods.

RESULTS

All participants performed preference, performance, and learning blocks of tasks, in that order. For each block (preference, performance, or learning tasks), we only report model-based analyses in the main text; the model-free analyses (as well as additional model-based analyses) can be found in the Supplemental Results. Note that with our sample size, only moderate to large effects (Cohen's $d > 0.68$) could be detected at standard statistical thresholds (power of 80% and significance level at 5%).

Preference Tasks

This block contained 4 tasks that presented the same natural items belonging to 1 of the following 3 dimensions: reward, punishment, or effort (Figure 1). Reward items could be food (e.g., to get a chocolate cookie) or goods (e.g., to get a standard 32-card deck) and punishment items could be sensory (e.g., to hear a chalkboard screech) or more abstract (e.g., to have my phone screen scratched), while effort items could be physical (e.g., to walk up 5 floors of stairs) or mental (e.g., to fill in an administrative form). Items were presented as short texts, except for an extra set of reward items that were accompanied by illustrative pictures.

In the likability rating task (Figure 1A), participants were instructed to rate how much they would like to be given the reward (likability rating of appetitive items) or how much they would dislike being imposed the punishment or effort (dislikability rating of aversive items). In the binary choice task (Figure 1B), participants were asked to select their favorite item from among 2 options belonging to the same dimension (i.e., the reward they prefer to obtain or the punishment/effort they prefer to endure). In the yes/no choice subtask (Figure 1C), they were asked to state whether they would accept or decline a hypothetical option representing a trade-off between 2 dimensions (exerting an effort to obtain a reward, exerting an effort to avoid a punishment, enduring a punishment to obtain a reward). Finally, in the intertemporal choice task (Figure 1D), participants were asked to state their preference between 2 hypothetical options combining 2 dimensions, i.e., an item associated with a delay. Thus, they had to choose between a small reward (or punishment or effort) being implemented immediately and a more likable (or less dislikable) one being implemented later in time.

Model-Based Analyses. The standard analysis of choice tasks consists of using a softmax function that transforms option values into selection likelihood, which is equivalent to logistic regression (Figure 1). When options are natural items with no explicit attribute such as magnitude or probability (Proba) of monetary gain or loss, option values are given by likability ratings. In the case of a binary choice between A and B, the $\mathrm{Proba_A}$ of selecting option A over option B ($\mathrm{Proba_B}$) is given by the softmax function as follows:

$$\mathrm{Proba_A} = \mathrm{sig}(\beta(\mathrm{Rating_A} - \mathrm{Rating_B})), \text{ with } \mathrm{sig}(x) = 1/(1 + \exp(-x))$$

where $\mathrm{Rating_A}$ and $\mathrm{Rating_B}$ are item A's and item B's likability rating, respectively. Here, slope β is a free parameter termed inverse temperature, which captures the consistency of choices; a higher β means fewer stochastic choices. Typically, the purpose of fitting such a choice model is to test whether ratings are good predictors of choices. However, this was not our case: We aimed at inferring the subjective values that patients assigned to the different items, given both likability ratings and choices. In that regard, the standard analysis is heavily biased: Likability ratings are assumed to be exact

Table 2. Comparison of Patients With MDD and Bipolar Disorder

Characteristic	MDD, *n* = 20	Bipolar Disorder, *n* = 15	*p* Value
Gender, Female/Male	11/9	7/8	.625
Age, Years	45.7 (19.0)	38.1 (12.9)	.192
Education, Years	14.8 (4.1)	15.8 (3.2)	.444
Currently Active[a]	11	9	.767
MADRS, Depression	37.2 (6.9)	34.7 (8.1)	.333
Starkstein, Apathy	23.7 (6.3)	24.0 (4.7)	.858
SHAPS, Anhedonia	5.6 (4.7)	5.1 (3.8)	.723
Thase and Rush Staging	2/7/6/5	4/8/3/0	.104
Lithium	0	6	.002
Antidepressant	20	4	<.001
Atypical Antipsychotic	5	10	.013
Anxiolytic	9	8	.625

Data are presented as *n* or mean (SD).

MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; SHAPS, Snaith-Hamilton Pleasure Scale.

[a]Including patients on sick leave and students.

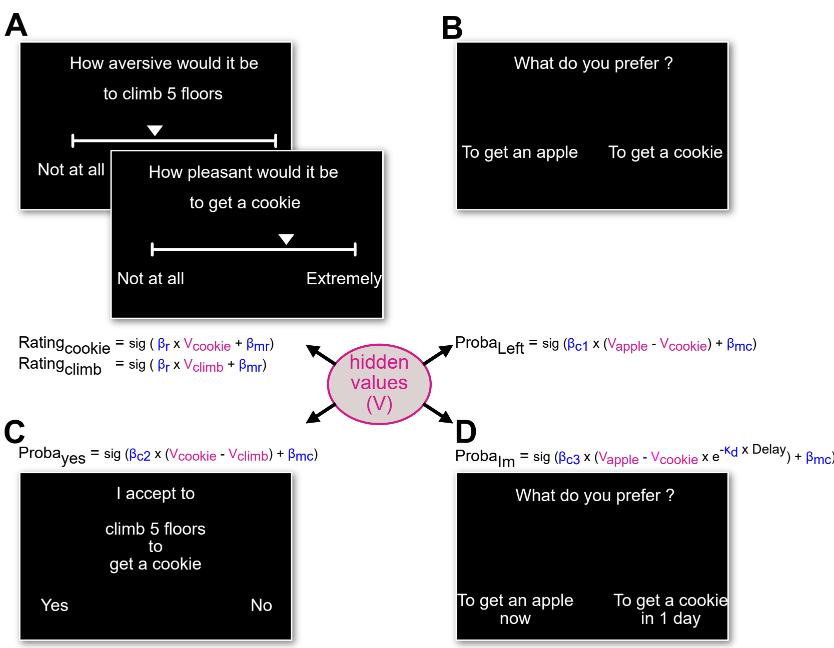


Figure 1. Preference block: task and modeling principles. Reward, punishment, and effort natural items were used in 4 tasks. **(A)** Rating task: participants were required to rate how appetitive rewards were (likability rating) or how aversive punishments and efforts were (dislikability rating). **(B)** Binary choice task: participants were required to choose between 2 items the one that they prefer. **(C)** Yes/no choice task: participants were required to hypothetically accept or decline an option combining 2 dimensions. **(D)** Intertemporal choice task: participants were required to make hypothetical choices between 2 items, 1 to be experienced immediately and 1 (more likable or less dislikable) after a delay. All behavioral outputs (ratings and choices) were fitted together using free parameters representing the hidden values (V_{item}, in pink) of the different items across tasks and free parameters (slope and bias, in blue) adjusting the sigmoid mapping specific to each task.

(noiseless) expressions of subjective values, whereas choices are assumed to be stochastic (noisy) expressions of those subjective values. A fair approach would consider both ratings and choices as noisy expressions of the same underlying hidden values (36). Thus, our general approach was to fit all tasks together with a unique model to extract these hidden values. Specifically, the subjective value of each item was represented by 1 free parameter. These hidden value parameters were then mapped through task-specific observation functions to produce the behavioral response (rating or choice). These functions contained other free parameters in addition to the hidden values, which were specific to the task but common to all dimensions. Thus, dimension-specific differences between groups could not be captured by task-specific parameters but only by the distribution of hidden values across the relevant set of items.

When fitted to all behavioral data concurrently, this computational approach provides estimates of 2 types of free parameters: hidden value parameters (1 per item) and task-specific parameters (weights, biases, and discount factors) that control the mapping from hidden values to behavioral responses (choices and ratings). For each participant and dimension, model inversion provided a distribution of hidden value parameters. The summary statistics (mean and variance) of value distributions (over items) were taken as measures of each participant's sensitivity to the different dimensions (reward, effort, and punishment).

Model-Based Results. Observed data and model fits for all tasks are illustrated in Figure 2. The distribution of hidden values across items and participants are illustrated in Figure 3A. The subjectwise mean hidden value was entered into analysis of variance with dimension as a within-subject factor, group (patients with MDE or HC subjects, respectively labeled as the MDE and HC groups) as a between-subject factor, and subject as a random factor (Figure 3B). There was a main effect of dimension ($p < .001$), indicating that our items were not balanced (i.e., punishments were more aversive than efforts). Beyond this, there was a main effect of group ($F_{1,68} = 4.7$, $p = .032$) and an interaction between group and dimension ($F_{2,136} = 3.8$, $p = .025$). Post hoc t tests revealed that this interaction was mainly driven by higher (i.e., more aversive) hidden values for effort items (μ_E) in the MDE group than the HC group (mean = 5.3 vs. 4.4, $t_{68} = 3.2$, $p = .002$), while there was no difference between the groups for all other dimensions. Higher hidden values in the MDE group were observed for both motor (mean 5.9 vs. 4.8) and cognitive (mean 4.8 vs. 3.9) efforts, both $p < .05$. The same analysis of variance was conducted on subjectwise standard deviation (across the set of items) and task-specific free parameters (see Supplemental Results and Figure S1 for details).

Thus, the main computational feature that distinguished the MDE group from the HC group was an increased aversion for effort cost (μ_E), which captured higher ratings of effort items and a higher tendency to avoid effort in yes/no choices (see the description of model-free analyses in Supplemental Results).

Performance Tasks

The abovementioned preference tasks suggest that the MDE group exhibited a higher sensitivity to effort than the HC group. However, these tasks are purely declarative because all options are hypothetical. To assess whether the same elevated effort sensitivity would manifest when the effort was not virtual and had to be exerted, we tested participants on performance tasks that were previously used in functional magnetic resonance imaging and

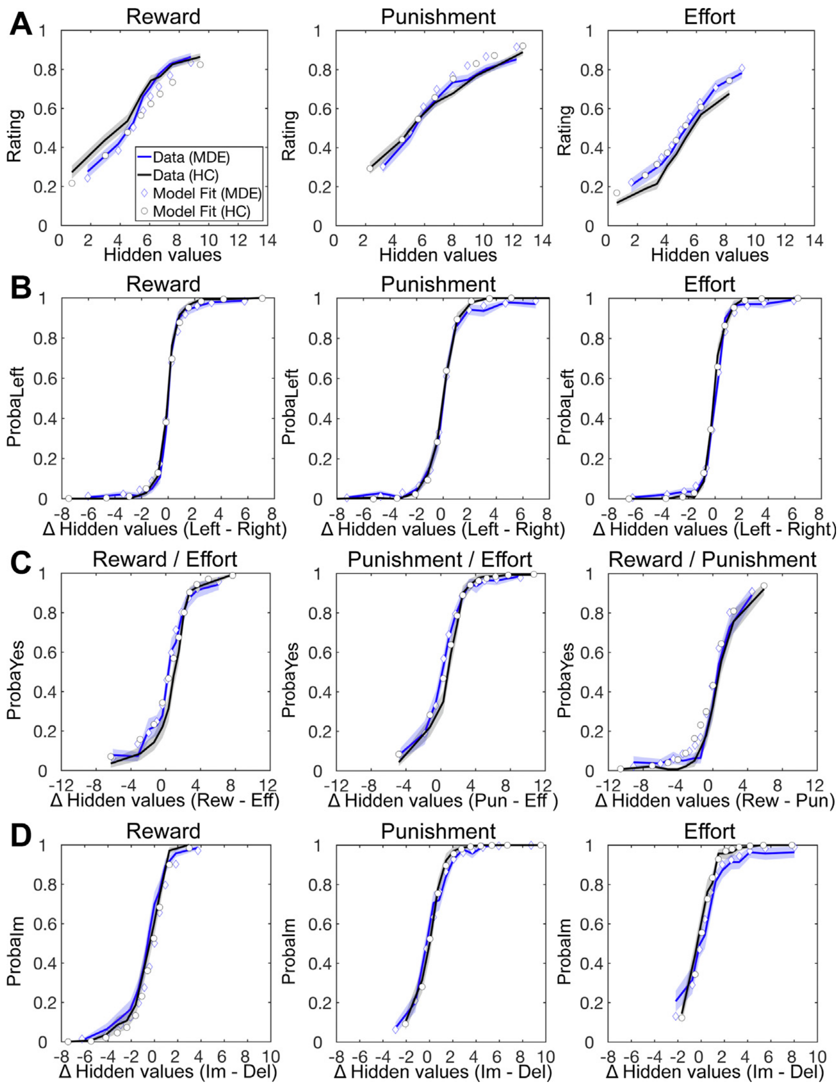


Figure 2. Preference block: model-free results and model fits. Observed data (lines) and model fits (diamonds) are shown for each of the 4 preference tasks. **(A)** Rating task: observed and modeled rating as a function of hidden value (inferred through model fitting) for reward (left panel), punishment (middle panel), and effort (right panel). **(B)** Binary choice task: observed and modeled choice rate (probability of choosing left) as a function of the difference between the left and right item value for reward (left panel), punishment (middle panel), and effort (right panel). **(C)** Yes/no choice task: observed and modeled choice rate (acceptance probability) as a function of the difference between the hidden values of benefit (obtained reward or avoided punishment) and cost (exerted effort or inflicted punishment) for the reward/effort (left panel), punishment/effort (middle panel), and reward/punishment (right panel) trade-offs. **(D)** Intertemporal choice task: observed and modeled choice rate (probability of choosing the immediate option) as a function of the difference between the hidden values of immediate and delayed items (using exponential discounting) for reward (left panel), punishment (middle panel), and effort (right panel). Shadows represent intersubject SEM. Del, delay; Eff, effort; HC, healthy control; Im, immediate; MDE, major depressive episode; Proba, probability; Pun, punishment; Rew, reward.

clinical studies (37,38). In both motor and cognitive performance tasks (Figure 4), participants exerted effort so as to maximize their (virtual) monetary payoff. Both tasks included 10 series of 12 trials in which participants played either to maximize monetary earnings or to minimize losses (on previously earned money). Each trial was associated with 1 of 6 possible monetary incentives (€0.01, €0.2, €0.5, €1, €5, or €20) corresponding to coins and notes used in everyday life in France. In the motor performance task, participants squeezed a handgrip, while in the cognitive performance task, they performed a series of numerical comparisons between digits displayed with different font size, generating a Stroop effect. Participants were instructed that the payoff was proportional both to the incentive at stake and to their performance (peak of force pulse in the grip task or number of correct responses in the Stroop task).

Model-Based Analyses. We used the same model to fit raw performance measures in the grip and Stroop tasks, namely peak force (in newtons) and correct response rate (number per second), respectively. This model was already applied to fit motor performance in a previous study that specified the computational phenotype of motivational deficit in patients with Parkinson's disease (37) and was extended to fit cognitive performance in this study (Figure 4; see Supplemental Methods and Figure S2 for details).

Model-Based Results. Observed data and model fits for all tasks are illustrated in Figure 5.

When comparing parameter estimates between groups (Figure 6), the most striking difference was a higher K_c (sensitivity to effort cost) in patients relative to control subjects for both motor performance (0.108 vs. 0.028, $t_{68} = 6.0$, $p < .001$) and cognitive performance (0.014 vs. 0.009, $t_{68} = 2.8$, $p =$

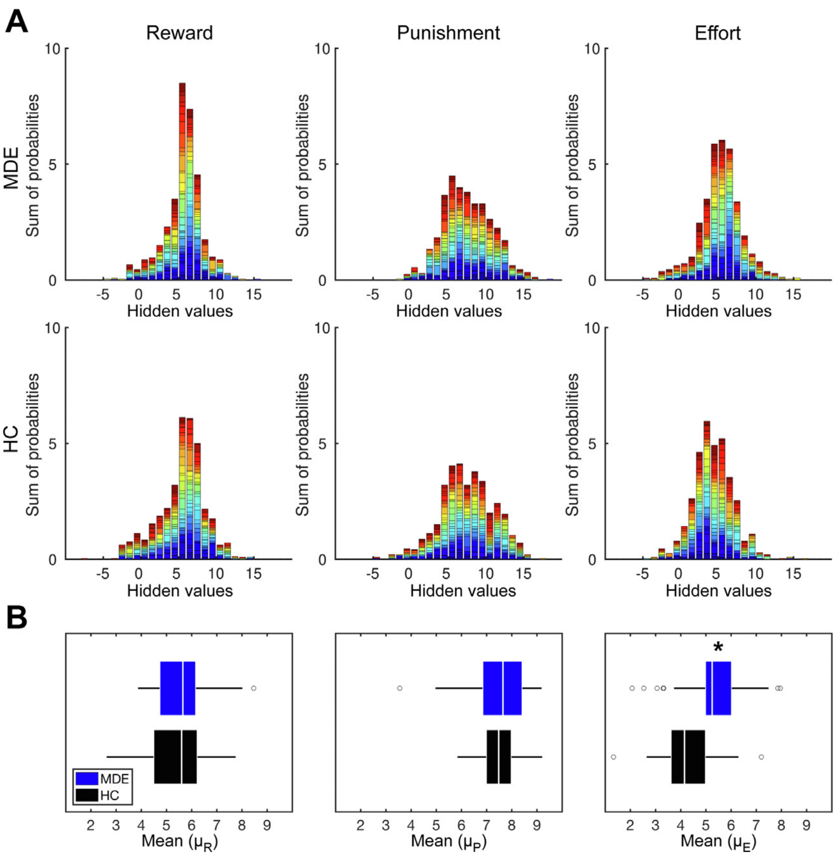


Figure 3. Preference block: model-based results. Stacked histograms of hidden values for both groups (patients with depression and healthy control [HC] subjects on top and bottom panels, respectively) and all dimensions (reward, punishment, and effort on left, middle, and right panels, respectively). Each participant is represented by a different (arbitrary) color. **(B)** Mean hidden values for each dimension. The difference between groups was significant for the effort dimension only. White line: median; box 25th (Q1) and 75th (Q3) percentiles of the distribution over the group. Points: outlier participants for whom the mean was larger than Q3 + 1.5 × (Q3 − Q1) or smaller than Q1 − 1.5 × (Q3 − Q1). Whiskers min to max (without outliers). *Significant at $p < .05$. μ_E, mean hidden value for effort; μ_P, mean hidden value for punishment; μ_R, mean hidden value for reward; max, maximum; MDE, major depressive episode; min, minimum.

.006). There was also a trend for lower K_i (sensitivity to incentive value), but it was not significant in motor performance (0.743 vs. 1.001, $t_{68} = -1.4$, $p = .172$) and bordered on significant in cognitive performance (0.004 vs. 0.012, $t_{68} = -2.0$, $p = .054$). Finally, P_{max} was lower in the MDE group than in HC subjects for both the grip (326 vs. 443 N, $t_{68} = -2.8$, $p = .006$) and the Stroop (1.71 vs. 2.3 correct responses/s, $z = -4.1$, $p < .001$) tasks. There was no significant difference between groups in K_f (fatigue effect).

Thus, the main computational feature that distinguished the MDE group from the HC group was an increased aversion for effort cost (K_c), which captured a globally lower motor and cognitive performance (see description of model-free analyses in Supplemental Results).

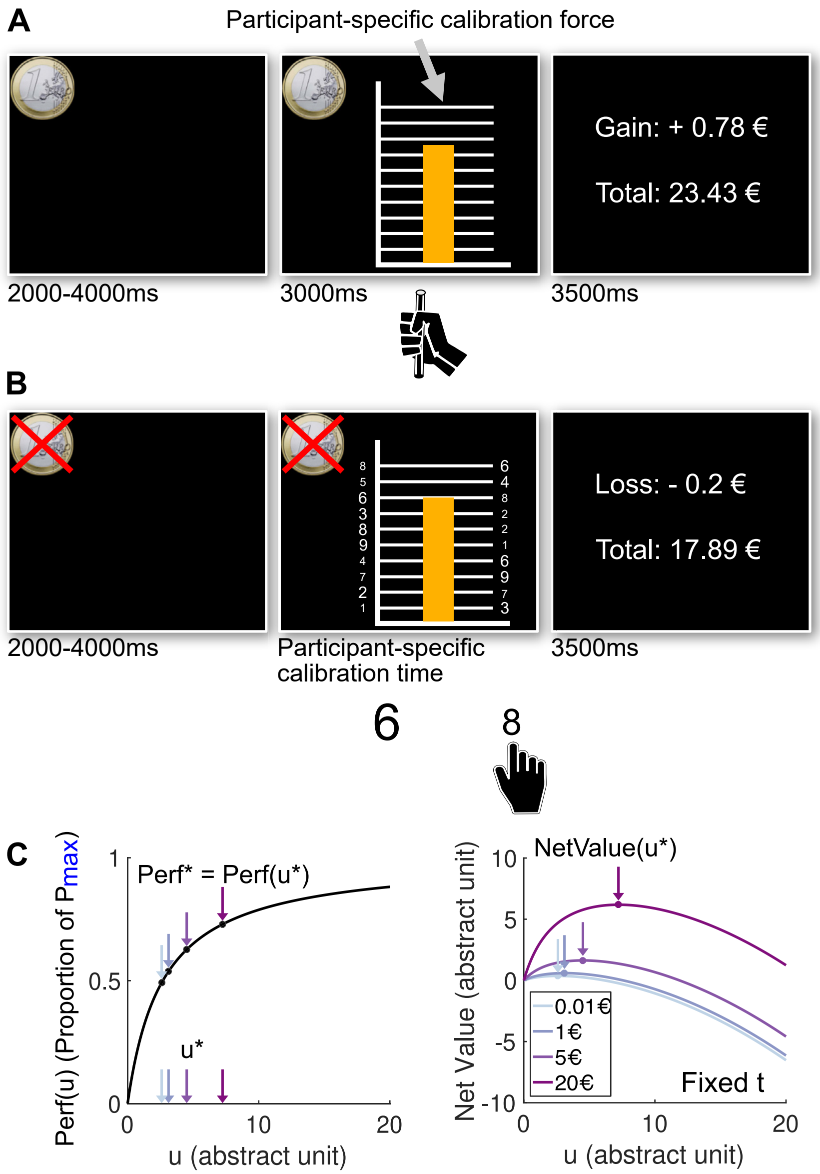
Learning Task

In the last block, participants performed 3 sessions of the same instrumental learning task, which had been used previously in functional magnetic resonance imaging and pharmacological studies to dissociate between positive and negative reinforcement (by reward and punishment). We observed no such dissociation, and the main distinction between groups was about choice stochasticity (see the Supplement for detailed results).

Link With Clinical Factors

Three clinical scores, depression severity (Montgomery–Åsberg Depression Rating Scale), apathy (Starkstein Apathy scale), and anhedonia (Snaith-Hamilton Pleasure Scale), were regressed against a general linear model containing mean hidden values for reward and effort items (μ_R and μ_E) in preference tasks. There was a significant link between the effort parameter and the apathy score, with more aversive effort value predicting more severe apathy ($\beta = -0.36$, $p = .032$). However, this association requires confirmation in larger samples because it would not survive correction for multiple comparisons if considering all possible links between computational parameters and clinical scores (there was no other significant link). Similarly, correlations between tasks (e.g., between parameters fitted to preference vs. performance tasks) failed to reach significance. In particular, there was no significant correlation between mean value for effort items and the weight of (motor or cognitive) effort cost (both $p > .1$).

Our sample of patients was diverse in terms of diagnosis (unipolar vs. bipolar disorder) and medication (antidepressants/anxiolytics/atypical antipsychotics/lithium), and it was too small for conducting direct comparisons between subgroups. However, the main results (elevated mean effort value μ_E and effort cost K_c relative to HC subjects) were



$$\mathrm{Perf}(u) = \frac{u}{u + \tau}$$

$$\mathrm{NetValue}(u,t) = \frac{\mathrm{Perf}(u)}{P_{max}} + K_i \times \frac{\mathrm{Perf}(u)}{P_{cal}} \times \mathrm{Inc}(t) - K_c \times \left(1 + K_f \times \frac{t}{N_t}\right) \times u^2$$

$$\mathrm{Perf}^* = \mathrm{Perf}\,(u^*) = \mathrm{Perf}\,(\underset{u}{\mathrm{argmax}}(\mathrm{NetValue}))$$

Figure 4. Performance block: task and modeling principles. In these performance tasks, participants had to produce an effort (either motor or cognitive) so as to maximize their (virtual) monetary payoff. Each trial was associated with 1 of 6 possible monetary incentives (€0.01, €0.2, €0.5, €1, €5, or €20). In both tasks, visual feedback on current performance level was provided as a cursor moving up a scale. **(A)** In the motor performance task, participants had to squeeze a handgrip as hard as possible within a 3-second time window. The top of the scale corresponded to maximal force produced during calibration. **(B)** In the cognitive performance task, participants had to perform as many as possible numerical comparisons between digits displayed with different font size, generating a Stroop effect. The time allowed was set to 70% of the time taken during calibration to complete all 10 numerical comparisons. The payoff was proportional to both the incentive at stake and participant performance (peak of force pulse in the grip task or number of correct responses in the Stroop task). Participants played either to win some money, as illustrated for the motor task in panel **(A)**, or not to lose previously earned money, as illustrated for the cognitive task in panel **(B)**. The feedback screen indicated both the money won or lost in the current trial and a cumulative total. **(C)** Cost-benefit optimization model. Simulated hidden variables. Perf (left part) is a saturation function linking resource spent (u) to performance F(u). F(u) tends to P_{max} (theoretical maximal performance) when u tends to ∞, without inflection point. The expected net value (right part) of possible resource investment u at a given trial t is obtained by subtracting costs from benefits (see main text and Figure S2 for details). The optimal resource u* and resulting perf and net value are illustrated in the graph for 4 of the 6 incentive levels. Free parameters are presented in blue. Perf, performance.

observed in all subgroups irrespective of the diagnosis and medication (Figure 7; see Supplemental Results for details). Thus, the findings were not driven by a particular subgroup and can be generalized across different types and treatments of MDE.

DISCUSSION

In this article, we used a series of behavioral tasks coupled with computational modeling to assess motivational deficits in patients with depression compared with matched HC subjects. More specifically, we assessed 3 key dimensions of

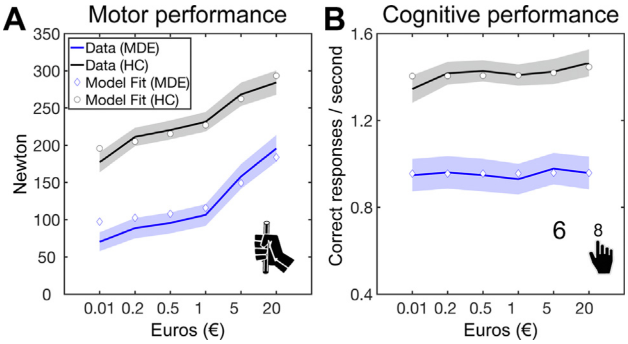


Figure 5. Performance block: model-free results and model fits. Observed raw performance (un-normalized) and modeled performance (diamonds) as a function of incentive level in the motor performance task (peak of force pulse in newtons, left panel) and in the cognitive performance task (rate of correct responses, right panel). Lines are means, and shadows represent intersubject SEM. HC, healthy control; MDE, major depressive episode.

motivational control that, in principle, could result in a reduction of goal-directed behavior: increased sensitivity to action costs (effort) and decreased sensitivity to action outcomes (reward and punishment). Even if we observed some reduced sensitivity to action outcomes, the most striking result was a massive increase in the sensitivity to effort cost, which we observed both in the preference tasks (mean aversive value of effort items, μ_E) and in the performance tasks (weight of effort cost on net expected value, K_c). In the following sections, we discuss the interpretation of computational parameters that were altered in our patients, possible links between our results and other conceptual frames for motivational control, and clinical implication of these results for pathological mechanisms and therapeutic interventions.

The typical approach in case-control studies of cognitive impairment is to use 1 behavioral task to assess 1 cognitive process. However, different tasks might be sensitive to different facets of the target process and present peculiarities that might bias the assessment (39,40). To better ensure that the results would be generalizable across contexts, we followed a conjunction method, looking for similarities rather than differences between tasks. In addition, we used a computational approach that distinguished task-specific parameters from the variables of interest that represent similar cognitive construct across tasks. Indeed, patients expressed an increased aversion for effort costs that was manifest in both preference and performance tasks. This is important because the 2 sets of tasks have different strengths and weaknesses. Performance tasks present the advantage of assessing the effort that patients really invest for goal-directed behavior (not just a declared intention to exert effort). They manipulate potential rewards in a systematic manner and provide objective performance measures, which indirectly quantify the effort invested. They have been extensively used to show a reduced willingness to exert effort for reward in patients with depression (25–29). Here, we replicate and extend this typical result by isolating the contribution of effort cost estimates from the impact of expected rewards. It is difficult to discriminate between possibilities of more aversive effort and more limited capacity (i.e., not willing to vs. not being able to). In other words, patients' reduced performance could rather be due to motor or cognitive capacity loss and not because doing the task properly would feel too effortful. Our strategy was to dissociate parameters that estimate maximal possible performance (i.e., capacity) from parameters that scale the expected cost to the expected benefit in the net value function that determines effort allocation (see the Supplement for a discussion devoted to this specific issue).

An increase in the aversiveness of both motor and cognitive effort cost was also observed in preference tasks. Compared with performance tasks, these rating and choice tasks present the advantage of directly assessing subjective effort costs. They also offer the possibility to generalize potential deficits to many different reward, punishment, or effort items that are faced in real life and not just motor and cognitive tasks made in the laboratory to win or avoid losing money. Thus, the

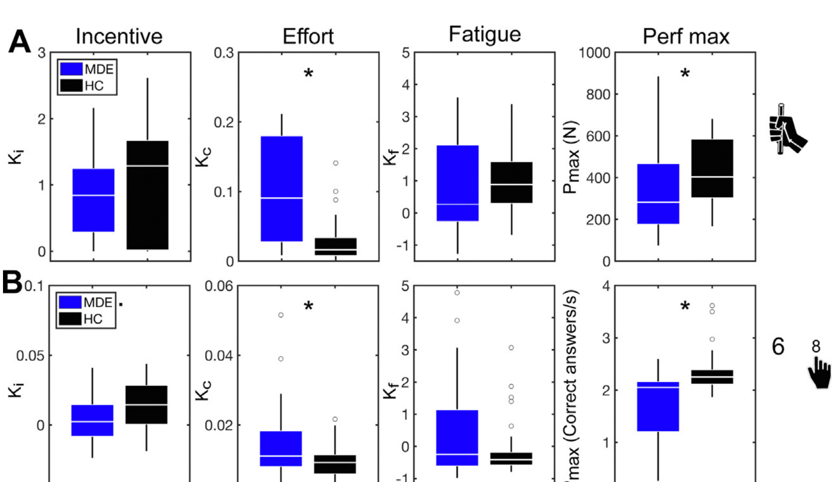


Figure 6. Performance block: model-based results. Summary statistics for the free parameters fitted on motor **(A)** and cognitive **(B)** performance. Difference between groups was significant for sensitivity to effort cost (K_c) and P_{max} (in both tasks) and marginal for sensitivity to incentive value (K_i) in the cognitive performance task. White line: median; box 25th (Q1) and 75th (Q3) percentiles of the distribution over the group. Points: outlier participants for whom the standard deviation was larger than Q3 + 1.5 × (Q3 − Q1) or smaller than Q1 − 1.5 × (Q3 − Q1). Whiskers: min to max (without outliers). *Significant at $p < .05$. HC, healthy control; K_f, fatigue effect; max, maximum; MDE, major depressive episode; min, minimum; Perf, performance.

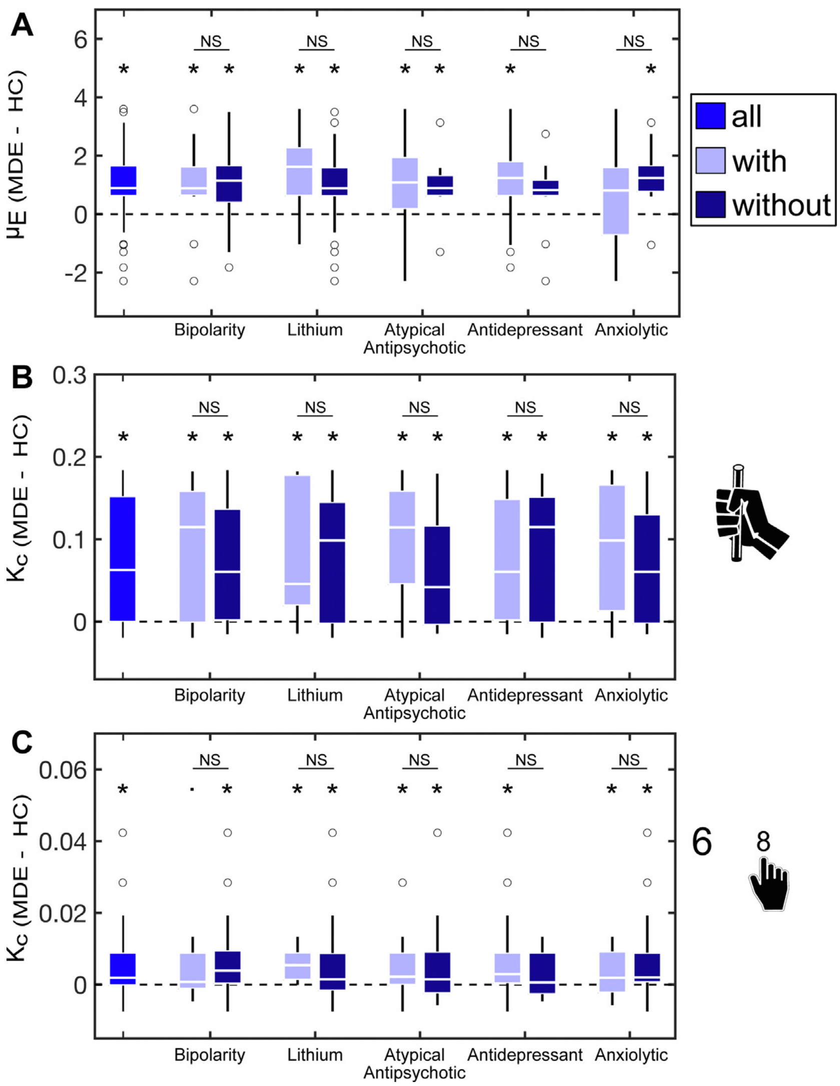


Figure 7. Effect of the diversity of patients and treatments on effort parameters. Summary statistics of mean hidden value for effort (μ_E) and sensitivity to effort cost (K_c) (in both tasks) as a function of diagnoses and treatments (boxplot of patients minus the average of healthy control [HC] subjects). For each parameter, we represented the whole major depressive episode [MDE] group (medium blue) and each subgroup separately (light and dark blue). For most factors of diversity, the difference from control subjects followed the same trend in the 2 subgroups (with and without the considered factor) and was significant in most cases. None of the direct comparisons between subgroups was significant. White line: median; box 25th (Q1) and 75th (Q3) percentiles of the distribution over the group. Points: outlier participants for whom the standard deviation was larger than Q3 + 1.5 × (Q3 − Q1) or smaller than Q1 − 1.5 × (Q3 − Q1). Whiskers: min to max (without outliers). *Significant at $p < .05$. max, maximum; min, minimum; NS, not significant.

observed enhanced effort sensitivity across preference and performance tasks provides strong evidence that this unique alteration explains both what patients feel (and report) and what they actually do when faced with a motor or cognitive challenge. However, we did not find a between-task correlation (across patients) in our measures of effort sensitivity (μ_E and K_c). Although this may be due to the limited sample size, it could also suggest that subjective effort costs in declared intentions (preference tasks) and in effective trade-offs (performance tasks) are partially dissociable (41).

Contrary to effort sensitivity, reward and punishment sensitivity did not differ much between patients and control subjects. Notably, there was no difference in the mean values of reward and punishment items (μ_R and μ_P) in preference tasks. The enhanced effort sensitivity, while outcome sensitivity is relatively preserved, is reminiscent of the preserved liking versus impaired wanting that has been observed in many conditions, including depression and anhedonia (27,42,43). Our tasks did not enable the systematic comparison of motivation and consumption phases that is required to specifically test the liking/wanting dissociation. However, our findings may shed new light on this dissociation, which was originally tested in rodents (44) by comparing the affective reactions to reward delivery (liking) and the willingness to exert effort for obtaining reward (wanting). Thus, at the heart of "wanting" is the trade-off between reward and effort that we have tested in our performance tasks. Under this view, our results provide complementary evidence for the notion that at least in some cases, impaired wanting could simply be reduced to excessive sensitivity to effort costs.

Even if decreased outcome sensitivity (in patients vs. control subjects) was sometimes bordering on statistical significance, it was always similar for reward and punishment, whether the task was about preference, performance, or learning. This is an important result because many studies have emphasized that low mood might lead to overweighting negative stimuli relative to positive stimuli (45–47). Typical results involve excessive processing of negative stimuli and higher sensitivity to negative feedback, possibly leading to learned helplessness, and a lower sensitivity to positive feedback associated with anhedonia (14,22,48). Our results instead single out effort cost as the distorted negative dimension (that shifts downward the expected net values driving actions) in depression. Comparatively, patients' processing of the other negative dimension (punishment) was not altered. In other words, the critical line of divide between people with depression and people without depression may not be between positive and negative events, but between action costs and outcomes (irrespective of whether they are anticipated or experienced).

Obviously, we do not claim that effort sensitivity is the only dimension that is affected in all patients with depression. This claim cannot be derived from our data, one reason being that it would be based on null results and another being that our results are limited to the factors tested in the behavioral tasks and to a small sample of patients who may not be representative of patients with depression in general. However, our results do suggest that sensitivity to effort cost is significantly more reliably affected than sensitivity to the other dimensions tested, which is important because previous studies using reward/effort trade-off tasks and models did not distinguish between these 2 possible explanations of apathy in depression—rewards feeling less desirable and effort feeling more exhausting.

A limitation of our study was the absence of strong correlations between the key computational markers of depression and the clinical dimensions assessed with questionnaires. This is in line with previous studies that failed to show a correlation between severity of depression and willingness to produce effort for reward (28,29). This suggests that computational modeling of behavior brings complementary information to standard questionnaires. Of course, this might not be the case if clinical scales used to score depression included more questions about how aversive effort is for patients in their daily lives. Moreover, we may not have the statistical power to test the correlation between clinical scores and computational parameters because our sample was modest in size and mainly composed of patients with severe depression (most of them being hospitalized when tested). The diversity in our sample may be seen not only as a weakness for drawing strong conclusions about a specific clinical feature, but also as a strength for a better generalization of the results, which is not possible when inclusion criteria are so narrow that all patients fall in the same subgroup. Indeed, we leveraged this diversity to show that our main findings (elevated aversion for effort relative to control subjects) were significant even when restricting the analysis to patients with a particular diagnosis or medication. Further studies may be needed to confirm our results in a more homogeneous sample of unmedicated patients.

Finally, computational phenotyping of motivational deficits may help bridge the gap between clinical assessment of depression and its underlying neurobiology. The link between dopaminergic transmission and sensitivity to reward has been studied extensively (49,50), including in reward/effort trade-off tasks (27,37,51–53), while punishment and sensitivity to losses have been linked with opioid transmission (54). The pharmacology of effort has seldom been explored (compared with pain and reward), but a recent study demonstrated that treatment with a classical antidepressant (citalopram) might help overcome effort cost (55), which would be consistent with the use of serotonergic medication in the treatment of depression. But if motivational deficits in patients with depression occur because of a salient increase in effort cost, then why are they weakly improved by serotonergic antidepressant treatment? A simple answer could be that patients' effort sensitivity is too high to be normalized by serotonergic medication. Alternatively, a minority of patients may have other deficits in addition to increased effort cost, including alterations of reward processing, which was shown to condition the response to antidepressant treatment (56,57). In the latter case, effort sensitivity would be a marker of the disease, while reward sensitivity would be a marker of drug resistance. Given the link between reward processing and dopaminergic transmission, individual patients with reduced reward sensitivity (on top of the common enhanced effort sensitivity) may be better treated with drugs that combine serotonergic with dopaminergic actions. Under this perspective, computational phenotyping of patients' motivational state would help predict which treatment should be used in each patient.

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ARTICLE INFORMATION

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